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## REMARKS

Claims 4-15, 18-23, 39, 40, 42- 47 and 49-56, are pending in the application, of which claims 39 and 40 are being amended.

Applicant thanks the Examiner for withdrawing the Section 112 and Section 102(e) and 102(a) rejections in view of the amendments of March 27th, 2006.

The Office Action indicated that "in response to applicant's argument that the instant claimed powder are not substantially aggregated, it is noted that the features upon which applicant relies are not recited in the rejected claim(s)." Claims 39 and 40 are now being amended to recite "a plurality of discrete particulate microstructures that exhibit decreased aggregation." This language is supported by the Specification at page 40, lines 4-5 ("decreases in particle aggregation") and line 21 ("discrete particles"). Thus no new matter is being added by these amendments and entry of the claim amendments is respectfully requested.

**Rejection Under 35 U.S.C. § 103(a) of Claims 4, 8-15, 18-23, 39-47, 49-50 and 55-56**

The Examiner rejected claims 4-15, 18-23, 39-47, 49-50 and 55-56 under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. (US 5,855,913) in view of Unger (6,120,751).

The Office Action stated "... in response to applicant's arguments that the instant claimed powder are not substantially aggregated, it is noted that the features upon which applicant relies are not recited in the rejected claim(s)." Applicant is now amending the claims to recite "an inhaleable powder composition comprising a plurality of discrete particulate microstructures that exhibit decreased aggregation". Thus, the distinguishing feature of the reduced aggregation of the discrete particulate microstructures is now recited in the claims.

The Office Action further recites that "it is pointed out that applicants claims to distinguish between the instant 'particulate microstructures' and aggregates since aggregates are particles". Applicant respectfully submits that the language of the amended claims now recites a plurality of discrete particulate microstructures that exhibit decreased aggregation to clearly distinguish aggregated particles from discrete particles which are separated from one another and not aggregated.

In view of the claim amendments, Applicant respectfully traverses the obviousness rejection. The present claims are patentable under Section 103(a) over Hanes et al. in view of Unger, because the cited combination of references does not establish a *prima facie* case of obviousness for the claims as amended. To establish a *prima facie* case of obviousness under 35 U.S.C. 103:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.,* 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

As amended, independent claim 39 claims an inhaleable powder composition comprising a plurality of discrete particulate microstructures that exhibit decreased aggregation, the microstructures having a structural matrix comprising an active agent, calcium, and a phospholipid, and a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm$^3$.

Claim 40 further recites that the particulate microstructures comprise a structural matrix comprising calcium, an active agent, and a phospholipid which has a gel to liquid crystal transition temperature of greater than 40°C.

Applicant respectfully submits that Hanes et al. and Unger references when considered as a whole do not teach or suggest the desirability, and thus the obviousness, of the present claims. As acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in particulate microstructures. Hanes et al. further teaches that particle aggregation is a problem, and also teaches the use of surfactants to reduce particle agglomeration. Hanes et al. also does not teach particulate microstructures having a mean aerodynamic diameter of less than 5 microns as claimed.

Unger should not be combined with Hanes et al. to support a 103 rejection because Unger does not motivate the application of calcium to the particles taught by Hanes et al. to derive discrete particulate microstructures that exhibit decreased aggregation, as claimed. Instead, Unger et al. teaches that the addition of calcium can result in particulate aggregation. Unger also does not make up for the deficiencies of Hanes, because Unger also does not teach particulate microstructures having a mean aerodynamic diameter of less than 5 microns as claimed.

In relation to the teachings of Unger, the Office Action states Applicant "has misconstrued Unger's use of the term 'aggregate'." Applicant respectfully disagrees. The Office Action cites Unger to teach at column 10:

> ... the counter ions (calcium) form salt bridges which crosslink the charged lipids to form aggregates **or** multilamellar vesicles. The aggregates **or** multilamellar vesicles may be referred to cochleates, which may be in the form of a tubule or a spiral. [Emphasis added.]

Applicant submits that the use of the alternative language "or" suggests that Unger teaches that the counter ions form bridging structures that form aggregates or multilamellar vesicles, and not that the aggregates and multilamellar vesicles are the same structures. If Unger intended to describe the same structures, Unger would not have used the alternative language "or" between aggregates and multilamellar structures.

Furthermore, in the second section relied on by the Office Action, namely at column 4, lines 45-54, Unger teaches that:

> 'Liposome' refers to a general spherical or spheroidal cluster or aggregate of amphiphatic compounds .... Liposomes formulated from non-ionic lipids may be referred to as niosomes. Liposomes formulated, at least in part, from cationic lipids or anionic lipids may be referred to as cochleates.

This language supports Applicant's arguments in that in this section, Unger teaches that cochleates are a type of liposomes, which in turn are clusters or aggregates of compounds. In the previously cited section, Unger teaches that and the aggregates or multilamellar structures can both be cochleates. Therefore, Unger is drawing a distinction between a multilamellar structure and an aggregate of such structures.

Furthermore, Unger teaches:

> Studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. Although the underlying physical causes for the phenomena are debatable, general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to **aggregate** into larger, multilamellar structures and promotes fusion. ...
>
> ... The effects of calcium-induced aggregation are so pronounced that efforts have been undertaken to limit the effect in order to control the size of liposomes used in drug delivery systems by forming vesicles in which calcium ions are confined to outer surfaces of the bilayer. ...

[Emphasis added]. (Unger, column 1, line 50 to column 2, line 9.) Thus, Unger teaches that calcium in the external environment of already formed phospholipid vesicles (a vesicle is a spherical structure) causes the already formed vesicle structures to aggregate together. Thus, Unger teaches that calcium causes aggregation of phospholipid vesicles. Such aggregation teaches away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures which exhibit reduced aggregation, as claimed. Thus, Unger does not motivate addition of calcium to the particulate structures taught by Hanes et al. to form discrete, non-aggregated structures,

but instead teaches that aggregation results from the addition of calcium to vesicle structures.

Furthermore, as taught in the present application, aggregation of particulate microstructures is undesirable as it reduces the dispersibility of the powder composition, which in turn affects how far the particulate structures travel into the pulmonary system. For example, the present Specification teaches:

> In order to maximize dispersibility, dispersion stability and optimize distribution upon administration, the mean geometric particle size of the perforated microstructures is preferably about 0.5-50 μm, more preferably 1-30 μm. It will be appreciated that large particles (i.e. greater than 50 μm) may not be preferred in applications where a valve or small orifice is employed, since large particles tend to aggregate or separate from a suspension which could potentially clog the device.

(Specification, page 32, lines 11-16.)

> With respect to the advantageous deposition profile provided by the instant invention it is well known that MDI propellants typically force suspended particles out of the device at a high velocity towards the back of the throat. Since prior art formulations typically contain a significant percentage of large particles and/or aggregates, as much as two-thirds or more of the emitted dose may impact the throat.

(Specification, page 39, lines 24-28.) Thus, the Specification teaches that aggregated particles are undesirable because they tend to separate from a suspension and clog the inhaler device. Also, as explained, prior art formulations such as those taught by Unger contain aggregates which result in a large percentage, as much as two-thirds or more of the emitted dose, impacting the throat and not traveling deep into the lungs, which is undesirable in inhalation therapy.

Thus, when considered as a whole, the Hanes et al. and Unger references do not teach the claimed inhaleable powder composition because the cited references do not teach or suggest, or motivate, the application of calcium to the particles of Hanes et al.. "In making the assessment of differences between the prior art and the claimed

subject matter, section 103 specifically requires consideration of the claimed invention 'as a whole.'" Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. (Fed. Cir., No. 04-1493, 6/9/05). "[S]imply identifying all of the elements in a claim in the prior art does not render a claim obvious. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). Hanes et al. makes no mention of calcium, teaches that particle aggregation is a problem, and further teaches the use of surfactants to reduce particle agglomeration. Unger teaches away from calcium addition to the particles of Hanes et al. because Unger teaches that calcium addition results in the aggregation of vesicles. Thus, the cited combination could only have been derived in hindsight based on Applicant's claim and the 103 rejection should be withdrawn because one of ordinary skill in the art would not have found it obvious to modify Hanes et al. based on the teachings of Unger.

It should be further noted that the cited combination of references also do not teach or suggest particulate microstructures having a mean aerodynamic diameter of less than 5 microns as claimed in claims 39 and 40. Instead Hanes et al. teaches that it is desirable to have particles with "a diameter within a selected range of at least 5 μm." For example, in column 7, lines 54 to column 8, line 67, Hanes et al. repeatedly emphasizes the desirability of particles sized at least 5 μm and in the range between about 5 and 30 μm. Thus, Hanes teaches away from, and does not motivate, the desirability of particles having a mean aerodynamic diameter of less than 5 microns, as claimed. Unger also does not teach or suggest particulate microstructures having a mean aerodynamic diameter of less than 5 microns as claimed. Instead, as acknowledged by the Office Action, Unger teaches larger sized particles, and also teaches aggregation of these larger particles by calcium addition.

Further, there is no reasonable expectation of success that the cited combination of references would operate as suggested by the Office Action. Specifically, Hanes et al. teaches that an organic solvent dissolved polymer is suspended in an aqueous medium containing a surface active agent, such as PVA, to form an emulsion that is stirred until the organic solvent evaporates to leave behind particles. If the particles made by this method were further aggregated with the addition of calcium to the aqueous medium, the resultant composition would have large aggregated particles which may well

have particle sizes larger than those described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences that Hanes et al. teaches against the use of a calcium aggregating agent as taught by Unger, and evidences the lack of motivation for this combination of references.

Furthermore, with respect to claim 40 and the claims dependent therefrom, neither Hanes et al. nor Unger teach particulates having phospholipid with a gel to liquid crystal transition temperature of greater than 40°C. Further, the teaching to a particular minimum gel to liquid crystal transition temperature is not obvious to one of ordinary skill simply from teachings that phospholipids are desirable to form particulate microstructures. Thus, when claim 40 is considered as a whole, the combination of Hanes et al. and Unger clearly do not teach or suggest claim 40 without the benefit of impermissible hindsight vision afforded by the claim itself. For these reasons, claim 40 and the claims dependent therefrom, are not rendered unpatentable by Hanes et al. in view of Unger.

For these reasons, claims 39 and 40 and their dependent claims are not rendered unpatentable by Hanes et al. in view of Unger. Accordingly, the Examiner is respectfully requested to allow the present claims.

**Rejection Under 35 U.S.C. § 103(a) of Claims 51-52**

The Examiner rejected claims 51-52 as being unpatentable over Hanes et al. in view of Unger and further view of Igarashi (4,201,774). This rejection is also respectfully traversed.

Claims 51 and 52 are to an inhalable powder composition in which bioactive agent is an aminoglycoside antibiotic. Claims 51 is dependent upon claim 40 and claim 52 is dependent upon claim 39.

As acknowledged by the Examiner, Hanes et al. does not teach the use of aminoglycoside antibiotic or calcium. Unger teaches that multivalent cations, such as calcium and magnesium, cause phospholipid vesicles to aggregate into larger, multilamellar structures and promote fusion between vesicles, as explained above. Unger

further teaches that certain species of phospholipids provide particularly pronounced aggregation effects. Thus, Unger teaches that calcium addition causes aggregation of phospholipid vesicles, and consequently, teaches away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures with reduced aggregation. The aggregation of phospholipid vesicles with calcium, as taught by Unger, would reduce dispersibility and dispersion stability of the particulate microstructures of the claimed composition. The aggregated particles would also potentially clog an inhaler device and have a greater tendency to impact the throat and provide less deposition into the deep lungs.

The Igarashi reference also does not teach or suggest particulate microstructures comprising phospholipid, calcium and an active agent, as claimed. Thus, the cited references do not provide any motivation to derive the claimed powder composition comprising particulate microstructures comprising phospholipid, calcium and an active agent as recited in claims 39 and 40.

Also, claims 39 and 40 both recite a powder composition comprising particulate microstructures having a mean aerodynamic diameter of less than 5 microns. In contrast, Hanes emphasizes the desirability of particles sized at least 5 μm. Thus, Hanes teaches away from the claimed mean aerodynamic diameter of less than 5 microns. Also, neither Unger nor Igarashi teach the desirability of particles having a mean aerodynamic diameter of less then 5 microns. Furthermore, Hanes et al., Unger and Igarashi do not teach particulate microstructures having a bulk density of less than about 0.5 g/cm$^3$ as claimed in claims 39 and 40.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 40. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, Applicant submits that claims 51 and 52 are allowable over the cited references.

**Rejection Under 35 U.S.C. § 103(a) of Claims 53-54**

The Examiner rejected claims 53-54 as being unpatentable over Hanes et al (US 5855913) in view of Cohen et al (5149543) in further view of Benson et al (5,006,343). This rejection is also respectfully traversed.

Claims 53 and 54 are to an inhaleable powder composition that includes a bioactive agent that is a fungicide. Claims 53 depends upon claim 39 and claim 54 depends upon claim 40.

Claims 53 and 54 are patentable for the same reasons as claims 39 and 40, respectively, from which they depend. As acknowledged by the Examiner, Hanes et al. does not teach the use of fungicides or calcium. Unger teaches that multivalent cations, such as calcium and magnesium, cause phospholipid vesicle structures to aggregate, and further teaches that phospholipids are particularly pronounced in these effects. Unger teaches away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures comprising phospholipid and calcium, because the aggregation of phospholipid vesicles with calcium would reduce dispersion stability of particulate microstructures. The aggregated particles have a greater tendency to undesirably impact the throat and provide less particle deposition into the lungs.

Benson also does not teach or suggest a particulate microstructure comprising phospholipid, calcium and an active agent. Thus the cited references do not provide any motivation to derive the claimed powder composition comprising discrete particulate microstructures comprising phospholipid, calcium and an active agent as recited in claims 39 and 40.

Also, claims 39 and 40 both recite a powder composition comprising particulate microstructures having a mean aerodynamic diameter of less than 5 microns.

In contrast, Hanes et al. emphasizes the desirability of particles sized at least 5 μm. Thus, Hanes et al. teaches away from the claimed mean aerodynamic diameter of less than 5 microns. Also, neither Unger nor Igarashi teach the desirability of particles having a mean aerodynamic diameter of less than 5 microns. Furthermore, Hanes et al., Unger and Igarashi do not teach particulate microstructures having a bulk density of less than about 0.5 g/cm$^3$ as claimed in claims 39 and 40.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to have particulate microstructures that include phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 40. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, the Examiner respectfully requested to allow claims 53 and 54 over the cited references.

**Provisional Double Patenting Rejections**

The provisional double patenting rejections will be addressed by the filing of a Terminal Disclaimer upon indication of allowable subject matter in the present application, since the double patenting rejection is provisional.

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

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